Cost-effectiveness of usual general practitioner care with or without antidepressant medication for patients with minor or mild-major depression

Bosmans, J.E.; Hennens, M.L.M.; de Bruijne, M.C.; van Hout, H.P.J.; Terluin, B.; Bouter, L.M.; Stalman, W.A.B.; van Tulder, M.W.

published in
Journal of Affective Disorders
2008

DOI (link to publisher)
10.1016/j.jad.2008.02.002

document version
Publisher's PDF, also known as Version of record

ELSEVIER

Journal of Affective Disorders 111 (2008) 106–112

Journal of Affective Disorders

www.elsevier.com/locate/jad

Brief report

Cost-effectiveness of usual general practitioner care with or without antidepressant medication for patients with minor or mild-major depression

Judith E. Bosmans [a,b,*], Marleen L.M. Hermens [c], Martine C. de Bruijne [a], Hein P.J. van Hout [c], Berend Terluin [c], Lex M. Bouter [d], Wim A.B. Stalman [c], Maurits W. van Tulder [a,b]

[a] *Health Technology Assessment Unit, Institute for Research in Extramural Medicine, VU University Medical Center, Amsterdam, The Netherlands*
[b] *Department of Health Economics and Health Technology Assessment, Institute of Health Sciences, Faculty of Earth and Life Sciences, VU University Amsterdam, The Netherlands*
[c] *Department of General Practice, Institute for Research in Extramural Medicine, VU University Medical Center, Amsterdam, The Netherlands*
[d] *Institute for Research in Extramural Medicine, VU University Medical Center, Amsterdam, The Netherlands*

Received 22 May 2007; received in revised form 31 January 2008; accepted 1 February 2008
Available online 14 March 2008

Abstract

Background: Minor depression is common in primary care and associated with increased health care costs. Many mildly depressed patients are prescribed antidepressants, although there is insufficient information on the cost-effectiveness of antidepressants for these patients. The objective of this study was to evaluate whether usual care without antidepressants is equivalent to (i.e. as effective as and as expensive as) usual care with antidepressants in patients with minor or mild-major depression.
Methods: Severity of depression was measured using the Montgomery Asberg Depression Rating Scale (MADRS) and quality-adjusted life-years (QALYs) using the EuroQol. Resource use was measured from a societal perspective using cost diaries. Bootstrapping was used to analyze the cost-effectiveness data.
Results: Equivalence could not be shown for improvement in MADRS score or QALYs gained at 52 weeks. The mean (95% CI) difference in total costs between usual care without antidepressants and usual care with antidepressants was −€751 (−3601; 1522). Using an equivalence margin of €500 equivalence in costs could not be shown. In the cost-effectiveness analyses equivalence also could not be shown.
Limitations: This study was underpowered for economic outcomes. Another limitation was the loss-to-follow-up.
Conclusions: Although equivalence could not be shown in the costs and cost-effectiveness analyses, 95% confidence intervals also did not show that usual care without antidepressants was vastly superior or inferior to usual care with antidepressants. Therefore, we recommend general practitioners to show restraint when prescribing antidepressants to mildly depressed patients.

Keywords: Depressive disorder; Costs and cost analysis; Antidepressive agents; Primary health care

* Corresponding author. VU University Amsterdam, Faculty of Earth and Life Sciences, Institute of Health Sciences; W&N Building, Room U435; De Boelelaan 1085, 1081 HV Amsterdam, The Netherlands. Tel.: +31 20 5982843; fax: +31 20 5983668.
E-mail address: judith.bosmans@falw.vu.nl (J.E. Bosmans).

0165-0327/$ - see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.jad.2008.02.002

1. Introduction

Mild forms of depression are common in primary care; prevalence estimates range from 3% to 5% (Katon and Schulberg, 1992). Minor depression is associated with impaired functioning and well-being, a raised number of disability days and raised health care costs (Broadhead et al., 1990; Johnson et al., 1992; Wells et al., 1989). Although there is insufficient evidence for the cost-effectiveness of antidepressants in patients with non-major depression (Ackermann and Williams, 2002; Elkin et al., 1989), general practitioners (GPs) in The Netherlands regularly prescribe antidepressants to these patients (Spies et al., 2004). Prescription of antidepressants in patients with non-major depression is only justified if they have additional benefits over usual care without antidepressants. Otherwise, disadvantages like medicalisation, side effects and dependence on antidepressants predominate.

Because absence of a statistically significant difference does not imply that the treatments being compared are equivalent (Altman and Bland, 1995), we chose to perform an equivalence trial to determine whether usual care without antidepressants (UCnoAD) by the GP is equivalent to (i.e. as effective as and as expensive as) usual care with antidepressants (UCAD).

2. Methods

2.1. Setting and participants

The trial was performed in The Netherlands in 2002 and 2003. The Medical Ethical Committee of the VU University Medical Center in Amsterdam approved the study protocol. The methodological details of the trial are reported in full elsewhere (Hermens et al., 2007).

Patients who were diagnosed with minor or mild-major depression (3–6 out of 9 DSM-IV depressive symptoms) by the GP, were eligible for the trial. Exclusion criteria were: age under 18 years, currently receiving antidepressants or psychological therapy, current psychosis, alcohol or drugs abuse, loss of a loved one or significant other in the past 6 months, pregnant or breastfeeding, and inability to complete questionnaires.

2.2. Design and randomisation

Economic data were collected alongside a randomised controlled trial with a follow-up of 52 weeks. Block randomisation was used to ensure equal numbers of patients in each treatment group per GP. Allocation schemes were generated by random number tables before the start of the trial. After the baseline interview, a member of the research team not in contact with the patient opened the appropriate opaque sealed envelope.

2.3. Interventions

All patients were scheduled for four 10–20 min consultations with their own GP at 2, 4, 7 and 11 weeks after inclusion (usual care). During these consultations patients received education, information, advice and support based on the guidelines for the treatment of depression of the Dutch College of General Practitioners (van Marwijk et al., 1994).

Patients allocated to UCAD, received paroxetine at a dose of 20 mg/day. Paroxetine was chosen because it was the most commonly prescribed antidepressant in The Netherlands at the time the study started (van Marwijk et al., 2001), and no clinically meaningful differences between antidepressants are found in primary care patients (MacGillivray et al., 2003).

During the first 3 months, GPs were asked not to deviate from the study protocol and to refrain from referral to mental health care providers, unless the GP judged this to be imperative. After 3 months, treatment could end or continue in the way the GP and patient preferred.

2.4. Outcome assessments

The severity of depressive symptoms was assessed using the Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). The MADRS was administered at 6, 13, 26 and 52 weeks of follow-up.

Health-related quality of life was measured with the EQ-5D (EuroQol) at baseline and 6, 13 and 52 weeks of follow-up (EuroQol Group, 1990). Quality Adjusted Life Years (QALYs) were calculated by multiplying the utility based on EQ-5D scores with the amount of time a patient spent in this particular health state (Dolan, 1997). Transitions between health states were linearly interpolated.

2.5. Cost measurement and valuation

The economic evaluation was conducted from a societal perspective. All resource use, informal care and absenteeism from paid and unpaid work were measured using cost diaries over a period of 52 weeks. Medication data were retrieved from the patient's pharmacy. Dutch standard costs were used to value resource use (Oostenbrink et al., 2002). Medication was valued using prices of the Royal Dutch Society for Pharmacy (Z-index, 2002).

All prices were adjusted for the year 2002 using consumer price index figures (Statistics Netherlands, 2007). Table 1 lists the cost categories and prices used in the economic evaluation.

We calculated the costs of absenteeism from paid work according to the friction cost approach (friction period 123 days) using mean age- and sex-specific incomes of the Dutch population (Koopmanschap and Rutten, 1996; Oostenbrink et al., 2000). According to this approach the amount of production lost due to disease is limited to the time span needed to restore the initial level of production. Costs of absenteeism from unpaid work were valued at a shadow price of €9 per hour which corresponds to the hourly rate of a legally employed cleaning lady.

Table 1
Costs used in the economic evaluation

	€ (2002 values)[a]
Direct healthcare costs	
Primary care costs	
General practitioner [per visit][b]	18
Blood test [per sample][b]	21
Urine analysis [per sample][b]	14
Social worker [per visit][c]	47
Psychologist [per visit][c]	75
Psychotherapist [per visit][c]	68
Physiotherapist [per treatment session][b]	20
Manual therapist [per treatment session][d]	31
Mensendieck therapist [per treatment session][b]	20
Dietician [per visit][c]	14
Chiropractor [per treatment session][c]	40
Company doctor [per visit][c]	21
Secondary care costs	
Psychiatrist [per visit][b]	62
Psychiatric admission [per day][b]	197
Outpatient visit [per visit][b]	45
Admission general hospital [per day][b]	260
Regional institute for mental welfare [per visit][b]	113
Light therapy [per treatment session][c]	43
Community care costs	
Professional home care[b]	25
Direct non-healthcare costs	
Alternative therapist[c]	Depending on type
Informal care [per hour][b]	9
Indirect costs	
Absenteeism paid labour [per day][e]	Depending on age and sex
Absenteeism unpaid labour [per hour][b]	9

[a] €1=.31.
[b] Guideline price according to Dutch guidelines.
[c] Price according to professional organisation or health care provider.
[d] Tariff of Dutch Central Organisation for Health Care Charges.
[e] Indirect costs for absenteeism from paid work calculated on mean income of Dutch population according to age and sex.

2.6. Equivalence margins for costs and effects

When performing an equivalence trial a relevant difference between the treatment groups (equivalence margin) has to be defined before the start of the study. (Jones et al., 1996) Because we examined equivalence of both effects and costs, we had to define a margin for both effects and costs. A margin of 5 was chosen for the difference in improvement in MADRS score at 52 weeks (Malt et al., 1999) and a margin of 0.03 for the difference in QALYs gained over 52 weeks (Lave et al., 1998). For costs, we defined 2 visits to the GP, 1 outpatient visit and 3 days of absenteeism from paid labour as a relevant difference (Kessler et al., 1999; Luber et al., 2000). After valuation of this difference using Dutch guideline prices, this resulted in an equivalence margin of €500.

2.7. Data analysis

Using the sample size calculation of Jones et al for equivalence trials (Jones et al., 1996), it was calculated that 84 patients per group were needed (2-sided $\alpha=0.05$, $\beta=0.10$) to detect a clinically relevant difference in improvement on the MADRS of 5 points. Clinical outcomes were analysed using independent *t*-tests. For the treatments to be equivalent, the 95% confidence interval (CI) around the difference in clinical outcome between the groups, should lie between the equivalence margins for this outcome.

CIs around the mean cost differences were estimated using bias-corrected and accelerated bootstrapping (2000 replications) (Efron and Tibshirani, 1993). UCnoAD was judged equivalent to UCAD, if the 95% CI around the difference in total costs was lying between −€500 and €500.

Uncertainty around the incremental cost-effectiveness ratios (ICERs) was estimated using the bias-corrected percentile bootstrapping method (5000 replications) (Chaudhary and Stearns, 1996) and presented on a cost-effectiveness plane (CE plane) (Black, 1990). The equivalence margins for costs and effects were presented on these planes. For UCnoAD to have equivalent cost-effectiveness compared with UCAD, 95% of the cost-effect pairs had to lie in the area within the equivalence margins. The equivalence margin for total costs may vary greatly in different settings or countries. We addressed this uncertainty by drawing an "equivalence curve". In this curve, the probability is drawn that UCnoAD is equivalent to UCAD (in other words, the

Table 2
Baseline characteristics of patients with complete cost data

	UCnoAD (n=44)	UCAD (n=45)
Age (years) [mean, SD]	48 (16)	46 (15)
Female [n, %]	32 (73%)	34 (76%)
Married [n, %]	28 (64%)	29 (64%)
Level of education [n, %]		
Low	12 (27%)	16 (36%)
Medium	19 (43%)	16 (36%)
High	11 (25%)	13 (29%)
Missing	2 (5%)	0
Duration depression >3 months [n, %]	27 (61%)	25 (56%)
PRIME-MD diagnosis [a]		
Minor depression	8 (18%)	8 (18%)
Mild-major depression	36 (82%)	36 (80%)
Missing	0	1 (2%)
MADRS score [mean, SD]	22 (10)	22 (9)
EQ-5D utility [mean, SD]	0.64 (0.26)	0.66 (0.23)

UCnoAD = Usual Care without Antidepressant; UCAD = Usual Care with Antidepressant; PRIME-MD = Primary Care Evaluation of Mental Disorders; MADRS = Montgomery Asberg Depression Rating Scale (range 0–60); EQ-5D = EuroQol.
[a] Minor depression=3–4 depressive symptoms and mild-major depression=5–6 depressive symptoms.

percentage of cost-effect pairs lying in the area between the equivalence margins) for various values of the equivalence margin for costs while the equivalence margin for effects is kept constant.

Intention-to-treat analysis usually makes the results from two treatment groups more similar and, thus, increases the chance of declaring equivalence. Therefore, a per-protocol analysis (PPA), which is expected to increase the contrast between the groups, was also performed (Jones et al., 1996). Patients in the UCnoAD group were included in the PPA if they received no antidepressant during the first 3 months of the trial, and patients in the UCAD group if they received at least 70 defined daily doses of an antidepressant during the first 3 months of the trial.

3. Results

Of the 117 participating GPs, 59 referred 293 eligible depressed patients, of whom 181 were included in the study (96 UCnoAD and 85 UCAD). Complete follow-up on all cost data was available for 89 (49%) patients. Patients with complete follow-up were more likely to be previously treated for depression or to have Dutch origins and were less depressed at baseline according to the MADRS. There were no differences in baseline sociodemographic and clinical characteristics between the two treatment groups for patients with complete follow-up (Table 2).

3.1. Clinical outcomes

Full details on the clinical outcomes are presented elsewhere (Hermens et al., 2007). In summary, equivalence could not be shown for the differences in improvement in MADRS score (mean absolute difference −0.81; 95% CI −5.6; 4.0) or QALYs gained (mean difference −0.00045; 95% CI −0.093; 0.084) at 52 weeks.

3.2. Costs

Table 3 shows the mean (standard deviation) costs for the two treatment groups. Although antidepressant costs in the UCnoAD group were significantly lower than in

Table 3
Mean (standard deviation) total costs (€) and differences in mean total costs (95% confidence intervals) during follow-up of 52 weeks for patients with complete cost data

	UCnoAD (n=44)		UCAD (n=45)		Difference	
Direct healthcare costs	1512	(1586)	1331	(1197)	181	(−386; 793)
Primary care costs	542	(492)	544	(557)	−2	(−228; 215)
Secondary care costs	437	(772)	335	(856)	102	(−302; 439)
Medication costs	423	(677)	423	(389)	−1	(−241; 226)
Professional home care costs	110	(393)	29	(145)	82	(−63; 164)
Direct non-healthcare costs	131	(248)	153	(316)	−22	(−138; 106)
Alternative therapy costs	57	(165)	8	(41)	48	(13; 80)
Informal care costs	75	(198)	145	(317)	−71	(−163; 54)
Total direct costs	1643	(1716)	1484	(1322)	159	(−498; 766)
Total indirect costs	3025	(5390)	3934	(5516)	−910	(−3224; 1461)
Costs absenteeism paid work	2807	(5150)	3506	(5379)	−698	(−2969; 1567)
Costs absenteeism unpaid work	217	(514)	429	(805)	−212	(−457; 88)
Total costs	4668	(5654)	5418	(6003)	−751	(−3601; 1522)

95% confidence interval obtained by bias-corrected and accelerated bootstrapping.
UCnoAD = usual care without antidepressants; UCAD = usual care with antidepressants.

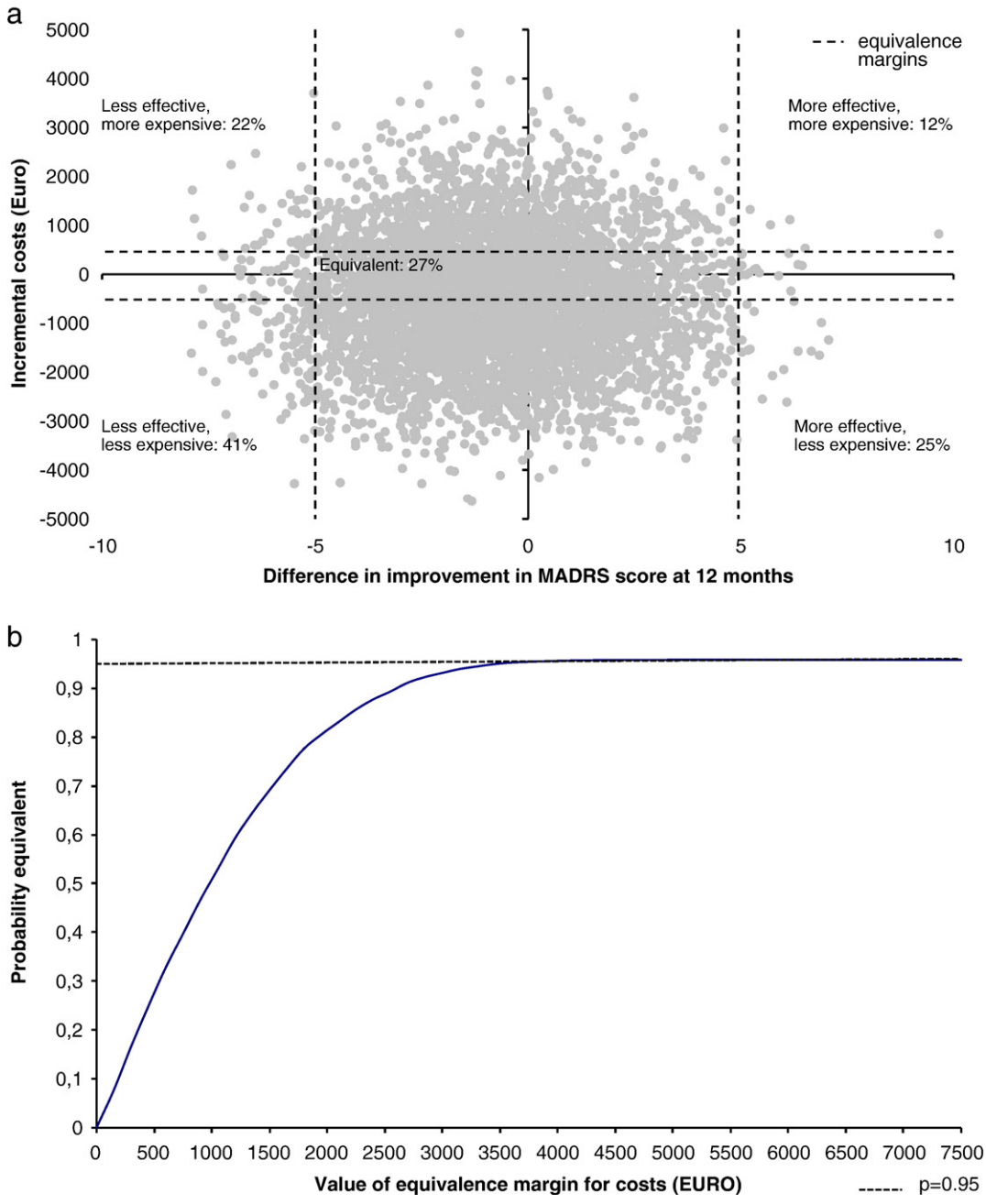

Fig. 1. a. Cost-effectiveness plane for improvement in Montgomery Asberg Depression Rating Scale (MADRS) score for usual care without antidepressants in comparison with usual care with antidepressants. The individual points on the plane represent 5000 bootstrapped cost-effect pairs using the bias-corrected percentile method. The central black dot indicates the point estimate of the incremental cost-effectiveness ratio. The dotted lines indicate the equivalence margins for costs and effects. b. Equivalence curve given an equivalence margin of 5 for improvement in Montgomery Asberg Depression Rating Scale (MADRS) score for usual care without antidepressants in comparison with usual care with antidepressants. In this curve, the probability is drawn that UCnoAD is equivalent to UCAD (in other words, the percentage of cost-effect pairs lying in the area between the equivalence margins) for various values of the equivalence margin for costs while the equivalence margin for effects is kept constant. The dotted line indicates a 0.95 probability that UCnoAD is equivalent to UCAD.

the UCAD group as expected (€66 versus €170; mean difference −104, 95%CI −158; −44), total medication costs were not statistically significantly different between the two treatment groups. Using an equivalence margin of €500, equivalence for costs could not be demonstrated.

3.3. Cost-effectiveness

The ICER for improvement in MADRS score was 594, meaning that one point of improvement extra on the MADRS in the UCAD group costs €594. Fig. 1a shows the CE plane for improvement in MADRS score for UCnoAD versus UCAD. Equivalence of UCnoAD in comparison with UCAD treatment could not be shown. Fig. 1b shows the equivalence curve for improvement in MADRS score at 52 weeks. It can be seen from this curve that UCnoAD is equivalent to UCAD for an equivalence margin of €3520. Equivalence of UCnoAD in comparison with UCAD for QALYs gained could also not be shown.

3.4. Per-protocol analysis

Thirty-two patients in the UCnoAD group and 34 patients in the UCAD group were included in the per-protocol analysis. Equivalence could not be shown for improvement in MADRS score or QALYs gained.

4. Discussion

It could not be demonstrated that UCnoAD was equivalent to UCAD in primary care patients with minor or mild-major depression. However, the difference in total costs was small in relation to the mean total costs. Presentation of 95% CIs allowed us to test for statistical superiority of UCnoAD versus UCAD. Although the 95% confidence limits included large cost differences in either direction, UCnoAD was not vastly superior or inferior to UCAD. Based on this and the disadvantages of antidepressant use, we recommend GPs to show restraint when prescribing antidepressants to patients with minor or mild-major depression.

As stated before, the equivalence margin for total costs may vary greatly in different settings or countries. Presentation of the CI around the cost differences allows readers to draw conclusions for margins that reflect their specific circumstances. Presentation of an equivalence curve makes it possible for readers to estimate the probability that UCnoAD is as effective as and as expensive as UCAD for an equivalence margin for total costs that better reflects their circumstances.

An important limitation is that our study was underpowered for economic outcomes which is reflected in the wide CIs. This is a common problem in economic evaluations. Because the distribution of cost data typically is heavily skewed, large numbers of patients are needed (Briggs, 2000). In equivalence trials even larger sample sizes are needed (Jones et al., 1996). However, it may be considered unethical to continue a trial beyond the point at which clinical superiority has been demonstrated (Briggs, 2000).

Another possible source of bias was the high loss-to-follow-up. However, similar results of an imputed analyses using the Expectation Maximization algorithm incorporated in SPSS 10.1 (SPSS Inc., 2000) suggest that the effect of this bias was limited.

5. Conclusion

Although equivalence could not be shown in the costs and cost-effectiveness analyses, 95% CIs also did not show that UCnoAd was vastly superior or inferior to UCAD. Considering the disadvantages of antidepressant use, we recommend GPs to show restraint when prescribing antidepressants to this group of patients. Future research should investigate the benefits of antidepressants for primary care patients with minor and mild-major depression further.

Role of funding source

The Dutch Health Care Insurance Board (DHCIB) financed the trial (grant number OG 00-020). The funding source had no involvement in the production of this manuscript; the views expressed in this paper are those of the authors only and are not attributable to the DHCIB.

Conflict of interest

The authors have no conflicts of interest directly relevant to the content of this study.

References

Ackermann, R.T., Williams Jr., J.W., 2002. Rational treatment choices for non-major depressions in primary care: an evidence-based review. J. Gen. Intern. Med. 17, 293–301.

Altman, D.G., Bland, J.M., 1995. Absence of evidence is not evidence of absence. BMJ 311, 485.

Black, W.C., 1990. The CE plane: a graphic representation of cost-effectiveness. Med. Decis. Making 10, 212–214.

Briggs, A., 2000. Economic evaluation and clinical trials: size matters. BMJ 321, 1362–1363.

Broadhead, W.E., Blazer, D.G., George, L.K., Tse, C.K., 1990. Depression, disability days, and days lost from work in a prospective epidemiologic survey. JAMA 264, 2524–2528.

Chaudhary, M.A., Stearns, S.C., 1996. Estimating confidence intervals for cost-effectiveness ratios: an example from a randomized trial. Stat. Med. 15, 1447–1458.

Dolan, P., 1997. Modeling valuations for EuroQol health states. Med. Care. 35, 1095–1108.

Efron, B., Tibshirani, R.J., 1993. An Introduction to the Bootstrap. Chapman & Hall, New York.

Elkin, I., Shea, M.T., Watkins, J.T., Imber, S.D., Sotsky, S.M., Collins, J.F., Glass, D.R., Pilkonis, P.A., Leber, W.R., Docherty, J.P., 1989. National Institute of Mental Health Treatment of Depression Collaborative Research Program. General effectiveness of treatments. Arch. Gen. Psychiatry 46, 971–982.

EuroQol Group, 1990. EuroQol—a new facility for the measurement of health-related quality of life. The EuroQol Group. Health Policy 16, 199–208.

Hermens, M.L., van Hout, H.P., Terluin, B., Ader, H.J., Penninx, B.W., van Marwijk, H.W., Bosmans, J.E., van Dyck, R., De Haan, M., 2007. Clinical effectiveness of usual care with or without antidepressant medication for primary care patients with minor or mild-major depression: a randomized equivalence trial. BMC Med. 5, 36.

Johnson, J., Weissman, M.M., Klerman, G.L., 1992. Service utilization and social morbidity associated with depressive symptoms in the community. JAMA 267, 1478–1483.

Jones, B., Jarvis, P., Lewis, J.A., Ebbutt, A.F., 1996. Trials to assess equivalence: the importance of rigorous methods. BMJ 313, 36–39.

Katon, W., Schulberg, H., 1992. Epidemiology of depression in primary care. Gen. Hosp. Psychiatry 14, 237–247.

Kessler, R.C., Barber, C., Birnbaum, H.G., Frank, R.G., Greenberg, P.E., Rose, R.M., Simon, G.E., Wang, P., 1999. Depression in the workplace: effects on short-term disability. Health Aff. 18, 163–171.

Koopmanschap, M.A., Rutten, F.F., 1996. A practical guide for calculating indirect costs of disease. Pharmacoeconomics 10, 460–466.

Lave, J.R., Frank, R.G., Schulberg, H.C., Kamlet, M.S., 1998. Cost-effectiveness of treatments for major depression in primary care practice. Arch. Gen. Psychiatry 55, 645–651.

Luber, M.P., Hollenberg, J.P., Williams-Russo, P., DiDomenico, T.N., Meyers, B.S., Alexopoulos, G.S., Charlson, M.E., 2000. Diagnosis, treatment, comorbidity, and resource utilization of depressed patients in a general medical practice. Int. J. Psychiatry Med. 30, 1–13.

MacGillivray, S., Arroll, B., Hatcher, S., Ogston, S., Reid, I., Sullivan, F., Williams, B., Crombie, I., 2003. Efficacy and tolerability of selective serotonin reuptake inhibitors compared with tricyclic antidepressants in depression treated in primary care: systematic review and meta-analysis. BMJ 326, 1014.

Malt, U.F., Robak, O.H., Madsbu, H.P., Bakke, O., Loeb, M., 1999. The Norwegian naturalistic treatment study of depression in general practice (NORDEP)-I: randomised double blind study. BMJ 318, 1180–1184.

Montgomery, S.A., Asberg, M., 1979. A new depression scale designed to be sensitive to change. Br. J. Psychiatry 134, 382–389.

Oostenbrink, J.B., Koopmanschap, M.A., Van Rutten, F.F.H., 2000. The Hague. Health Care Insurance Council, The Netherlands.

Oostenbrink, J.B., Koopmanschap, M.A., Rutten, F.F., 2002. Standardisation of costs: the Dutch Manual for Costing in economic evaluations. Pharmacoeconomics 20, 443–454.

Spies, T., Mokkink, H., De Vries Robbé, P., Grol, R., 2004. Huisarts kiest vaak voor antidepressiva onafhankelijk van de ernst van de depressie. Huisarts Wet 47, 364–367.

SPSS Inc., 2000. SPSS 10.1. SPSS Inc, Chicago, IL.

Statistics Netherlands, 2007. www.cbs.nl (Accessed January, 2008).

van Marwijk, H.W.J., Grundmeijer, H.G.L.M., Brueren, M.M., Sigling, H.O., Stolk, J., van Gelderen, M.G., Vintges, M., Eizenga, W.H., Burgers, J.S., 1994. Guidelines on Depression of the Dutch College of General Practitioners (NHG-Standaard Depressie). Huisarts Wet 37, 482–490.

van Marwijk, H.W., Bijl, D., Ader, H.J., De Haan, M., 2001. Antidepressant prescription for depression in general practice in The Netherlands. Pharm.World Sci. 23, 46–49.

Wells, K.B., Stewart, A., Hays, R.D., Burnam, M.A., Rogers, W., Daniels, M., Berry, S., Greenfield, S., Ware, J., 1989. The functioning and well-being of depressed patients. Results from the Medical Outcomes Study. JAMA 262, 914–919.

Z-index, 2002. The Hague. Z-index, The Netherlands.